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Second Malignant Tumours in Childhood Hodgkin's Disease

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This study was undertaken to determine the treatment-specific incidence of second malignant tumours (SMT) in childhood Hodgkin's disease. The institutional databases at The Hospital for Sick Children, the Princess Margaret Hospital, and the Toronto-Bayview Regional Cancer Centre were reviewed for the years 1958–1993. Three hundred and forty-three consecutive newly diagnosed children were evaluated. The overall 30 year cumulative SMT incidence was 31%. The 20 year SMT incidence was greater for patients who relapsed (n = 129), 27%, compared with patients who remained relapse free (n =214), 13%. For patients with stage 1–3B disease who remained relapse free, the 10 year SMT rate was 7% for patients who were surgically staged and treated with extended field radiation treatment (EF RT) (35 G), compared with 3% in clinically staged patients treated with MOPP (six cycles) and EF RT (25–30 G). To date there is no significant difference in the oncogenicity of these treatment protocols. However, EF RT alone was less effective in disease control. For stages 1–3B, 62% of patients relapsed after EF RT alone compared with 18% after bimodal treatment. Therefore treatment intensification due to relapse was more frequent in the former group. The overall 10 year SMT incidence for patients treated with these protocols was 11% and 3%, respectively. The 20 year SMT incidence following EF RT alone was 24%. We conclude that SMTs were a common late complication in childhood Hodgkin's disease and are a limiting factor in the achievement of cure. The incidence of SMTs was increased in children who required retreatment and was minimal in children who remained in a first complete remission. Therefore the initial treatment strategy in childhood Hodgkin's disease must be to minimize the risk of relapse, in order to avoid the morbidity and mortality associated with both relapse and SMT induction, and to achieve this objective with a primary treatment protocol of low oncogenicity.

Key words: Hodgkin's disease, childhood, second malignant tumours

INTRODUCTION

The 20 year incidence of second malignant tumours (SMTs) following the treatment of Hodgkin's disease in adults is 20%. The SMTs are acute leukemia (25%) non-Hodgkin's lymphoma (17%), and solid tumours (58%) [1]. An excess of tumours of the salivary glands, bronchus, pleura, skin, small and large intestines, bone, thyroid, breast, nasopharynx, melanoma, larynx, and cervix has been reported [1–2]. The relative risk of leukemia and non-Hodgkin's lymphoma plateaued at about 4% by 17 years, whereas the cumulative incidence of solid tumours increased progressively with time [1–4]. A lower SMT rate was seen in patients who remained continuously disease free [1,5] and in these patients combined modality therapy with radiation and MOPP, or MOPP-like therapy, was the dominant prognostic factor for acute leukemia induction, whereas for solid tumours radiation-alone or combined-modality therapy were significant factors. When deaths due to SMTs were censored, there was an 11% increase in long-term survival [1]. Today, 75% of newly diagnosed adult patients can expect to be cured of Hodgkin's disease [6], so that the relative importance of SMTs as a limiting survival hazard has increased.

There are few data regarding the frequency of SMTs after the diagnosis of malignancy in childhood. The overall second cancer risk for 9,170 children with all diagnoses made from 1945 to 1979 and registered at institutions contributing to the late effects study group (LESG) was 12% at 25 years [7]. A much lower rate of 4% at 25 years was reported from the United Kingdom in a national study of 10,106 3 plus-year survivors of childhood malignancy [8]. Intermediate rates were described at single institutions: in Paris (n = 634) 7.8% at 25 years [9] and in Buffalo (n = 1,406) 5.6% at 25 years [10]. The LESG has reported that the SMT rates in childhood Hodgkin's disease are the second highest, after retinoblastoma, among all primary childhood neoplasms [11]. Only 5% of SMTs in children are not associated with

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radiation treatment or chemotherapy [11]. University of Toronto patients were contributed to the LESG study of 979 children with Hodgkin's disease, diagnosed from 1955–1979. Thirty-eight SMTs were observed, for a 20 year incidence of 20% [12]. The common SMTs were 20 (53%) leukemia/lymphoma; thyroid cancer, basal cell carcinoma, and bone or soft tissue sarcomas 4 (11%) each; and 6 (16%) other cancers. The principal risk factor for leukemia/lymphoma was the use of alkylating agents. Splenectomy was of borderline significance. In univariate analysis only, leukemia/lymphoma was seen more often in late stage Hodgkin's disease, although there was no similar effect for solid tumours. The overall risk of SMTs was not significantly related to recurrence when adjusted for alkylator score [12].

The current review was undertaken to determine, in a single institution, SMT rates in childhood Hodgkin's disease and, specifically, to evaluate the incidence of SMTs in patients with CS 1–3B disease treated by staging laparotomy with splenectomy and extended field radiation treatment (EF RT) alone, our practice from 1963 to 1972, and to compare this result with a subsequent cohort, from 1973 to 1986, treated bimodally, after clinical staging, with sandwich MOPP (six cycles) and moderate dose EF RT (25–30 Gy) [13].

METHODS AND MATERIALS

From 1958 to 1993, 343 consecutive children were registered at the Hospital for Sick Children (HSC), the Princess Margaret Hospital (PMH; 1958–1985), and at Toronto-Bayview Regional Cancer Centre (T-BRCC; 1986–1993), and received radiation treatment as part of their primary management. During these years, radiation treatment was omitted only for those stage 4 patients with diffuse disease, usually widespread bone involvement, in whom extended field irradiation of all known disease was not practical, and from 1983 to 1986 for 23 patients in all stages who were treated in a pilot study of chemotherapy alone. The hospital records at HSC, PMH, and T-BRCC were reviewed in January 1994 to obtain long-term follow-up data.

At diagnosis 334 (97%) patients were less than 17 years old, the normal cutoff age for admission to The Hospital for Sick Children. An additional nine patients, eight who were 17 years old and one who was 18 years old, were treated by the pediatric lymphoma group using the same protocols and were included in the analysis. The overall Ann Arbor clinical stage distribution (and number of patients per stage) was 1A (21%) 73, 1B (1%) 5, 2A (35%) 119, 2B (11%) 38, 3A (9%) 31, 3B (6%) 19, 4A (7%) 23 and 4B (9%) 32. Three patients had inadequate data for staging.

For 337 patients with complete treatment data, 141 (42%) patients were treated initally by irradiation alone and 196 (58%) were treated bimodally with systemic agents and radiation treatment. For all patients (n = 343) the 10, 20, and 30 year unadjusted, or crude, survival rates were 75%, 66%, and 53%. For patients alive at last follow-up, the survival range was 1–36 (median 11) years and the patient-years of follow-up were 2,960. Eighty-eight (26%) of these patients have died: 56 (16%) due to progressive Hodgkin's disease, 19 (6%) due to treatment toxicity, 11 (3%) due to a SMT, and 2 patients due to causes unrelated to Hodgkin's disease or its treatment. Two hundred and fifty-five patients were alive at last follow-up, and their age at that time was 7–52 (median 25) years. At that time 217 (85%) were in regular clinic attendance, 33 (13%) had paper follow-up information, and 5 (2%) were lost to follow-up. The patients "lost" were followed for 1–21 (median 13) years before their lost to follow-up status was assigned. Overall, for patients diagnosed prior to 1990, 80% of surviving patients were last seen in clinic within 2 years of the review date and 91% were seen within 4 years.

The principal treatment protocols for stage 1–3B disease were [13,14] as follows:

1958–1962 Clinical staging. Involved field radiation treatment (IF RT). Single agent chemotherapy ± radiation treatment at relapse. (n = 21).

1963–1972 Surgical staging with splenectomy. EF RT (35 Gy). MOPP ± RT at relapse. (n = 76).

1973–1983 Clinical staging. Bimodal treatment. MOPP (six cycles) and EF RT (25–30 Gy). Favourable clinical stage 1A, IF RT (35 Gy). ABVD or MOPP ± RT at relapse. (n = 90).

1987–1993 Clinical staging. Bimodal treatment. MOPP/ABV (three cycles), EF RT (15 Gy). Favourable clinical stage 1A, IF RT (35 Gy). (n = 51).

Thus, 238 of 285 (83%) patients with CS 1–3B disease were treated on protocol, and 47 patients were treated by other methods. The unadjusted 20 year survival rate for patients with CS 1–3B disease treated during 1963–1972 by splenectomy and irradiation was 56% and treated during 1973–1983 bimodally was 87%. Patients with stage 4 disease were treated by various single systemic agents with or without irradiation prior to 1964 and, subsequently they were initially treated with MOPP, generally associated with EF RT. In 1987, MOPP was replaced by MOPP/ABV. The 20 year survival rate for 55 stage 4 patients was 64%.

Survival estimates were computed using the method of Kaplan-Meier. Survival estimates included all causes of death, unless otherwise stated. Estimates of SMT cumulative incidence were also derived using the method of Kaplan-Meir, with patients without SMT censored at the time of last follow-up. Comparison of survival curves

TABLE I. Second Malignant Tumours That Occurred in 343 Children with Hodgkin's Disease, Diagnosed from 1958 to 1993

Acute leukemia	6
Basal cell carcinoma	5
Thyroid carcinoma	4
NHL	2
Melanoma	2
Breast cancer	1
Sarcoma	1
Colon cancer	1
Histiocytosis X	1
Parotid cancer	1
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NHL = non-Hodgkin's lymphoma.

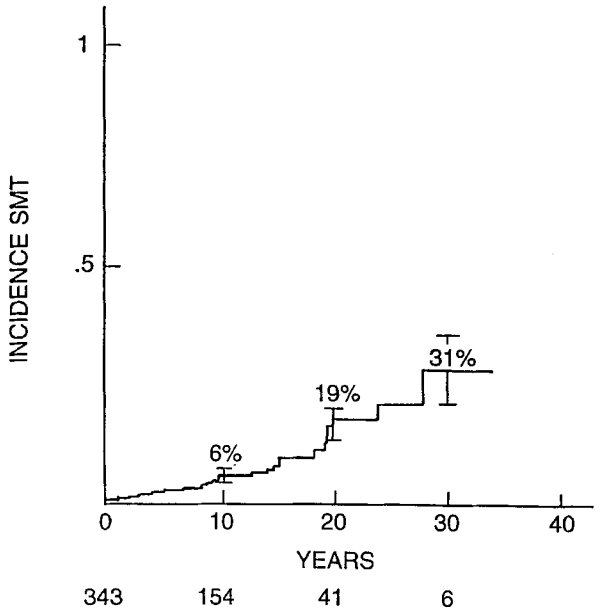

Fig. 1. SMT cumulative incidence, for 343 consecutive children, in all stages, irradiated for Hodgkin's disease from 1958 to 1993. Standard errors are indicated.

was made using the long-rank (Mantel-Haenszel) test. Multivariate analysis utilized Cox's proportional hazards regression method.

RESULTS

All Patients

Twenty-four of 343 (7%) patients have developed a SMT (Table I). Two patients have, in addition, developed third malignant tumours, basal cell cancer, and squamous skin cancer. Overall the 10, 20, and 30 year cumulative actuarial incidences of SMT were 6%, 19%, and 31% (Fig. 1). The incidences of acute nonlymphocytic leukemia (ANLL) at 10, 20 and 30 years were 2%, 4%, and 4%, and of leukemia and NHL combined were 3%, 5%, and 5%, whereas the incidences of all other tumours were 3%, 15%, and 27%, respectively. (Fig. 2).

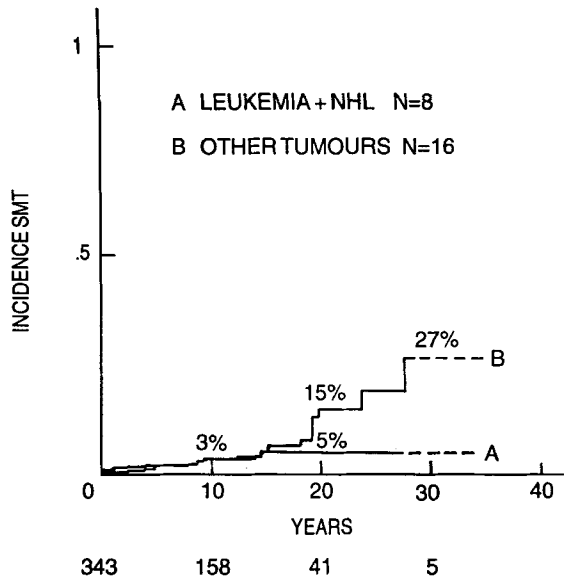

Fig. 2. Second malignant tumours. The cumulative incidence of leukemia non-Hodgkin's lymphoma (NHL) (**A**) and other tumours (**B**) is given.

The SMT incidence was significantly greater for patients with any relapse (n = 129), compared with those with no relapse (n = 214), with 20 year incidence rates of 27% and 13%, respectively ($P = 0.01$) (Fig. 3).

Stages 1–3B

For patients with stage 1–3B disease who were surgically staged and treated with EF RT (35 G), the 10 year and 20 year SMT incidences were 11% and 24%, respectively. For clinically staged patients treated with MOPP (6 cycles) plus EF RT (25–30 G), the 10 year SMT incidence was 3%. No patients treated since 1987 with three cycles of MOPP/ABV and EF RT (15 Gy) have developed a second malignant tumour (Fig. 4). For patients in the pathologically staged subset initially treated by EF RT (35 Gy) alone and who never relapsed (n = 29), the 10 and 20 year SMT incidences were 7% and 12%, compared with 14% and 37% for patients in this subset who survived following relapse (n = 47) (Fig. 5) ($P = 0.03$). For patients in the clinically staged subset, initially treated by MOPP (six cycles) plus EF RT (25–30 Gy), who never relapsed (n = 74), the 10 year SMT incidence was 3%. To date, there have been no SMTs among the patient's who survived following relapse (n = 16).

Multivariate Analysis

Multivariate analysis of these data for factors associated with SMT induction, using the variables relapse (yes/no), age (<14 and ≥ 14 years), stage (1–3B/4), and sex (male/female), indicated that relapse was the only significant variable ($P = 0.045$), followed by age

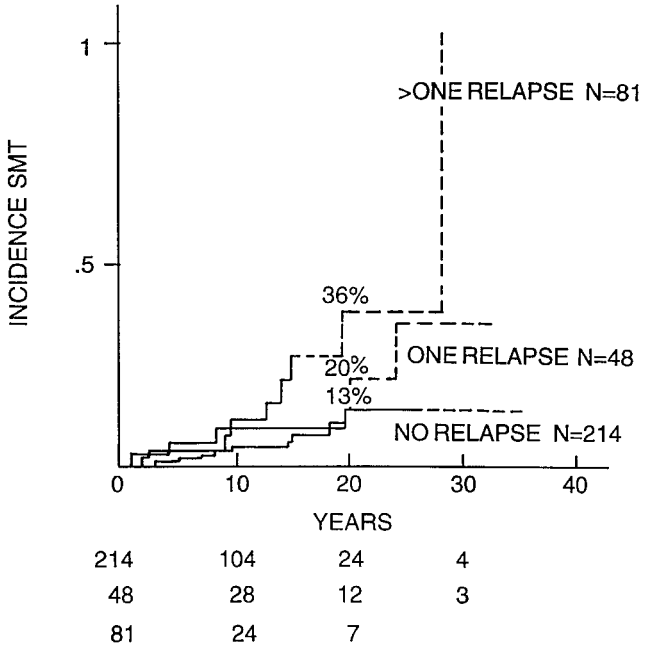

Fig. 3. Cumulative SMT incidence, for patients in all stages (n = 343), is given by relapse status at last follow-up for no relapse, one relapse (or progression), and more than one relapse. The hatched curve indicates that 10 or less patients were available for analysis.

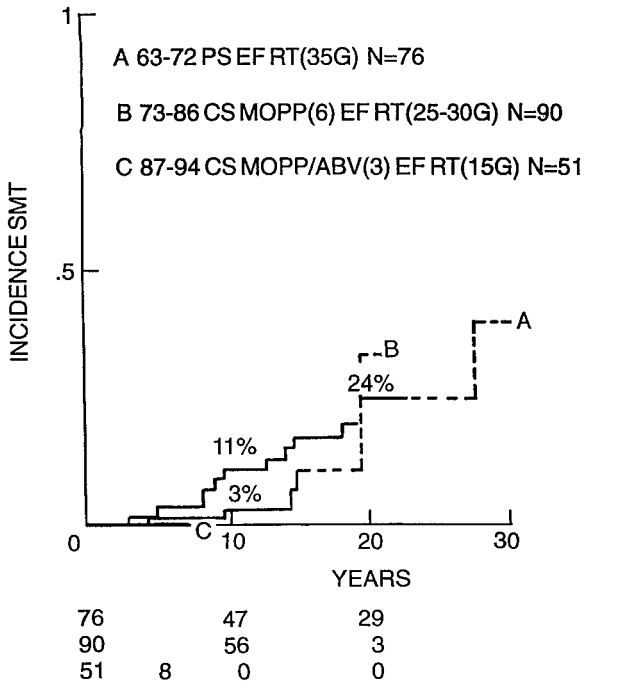

Fig. 4. Cumulative SMT incidence, for patients with stage 1–3B Hodgkin's disease, by treatment protocol.

($P = 0.11$). The inclusion of the variables splenectomy (yes/no) ($P = 0.09$) and the use of MOPP (yes/no)

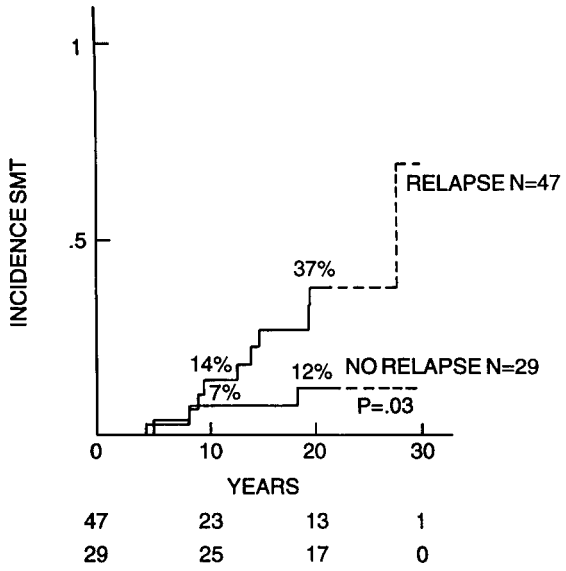

Fig. 5. Cumulative SMT incidence, for patients with stage 1–3B Hodgkin's disease treated by surgical staging, splenectomy, and EF RT (35 G), by relapse status at last follow-up.

($P = 0.11$) in initial treatment in the analysis did not materially change this finding.

Second Malignant Tumours

Leukemia was observed at 2–14 (median 9) years and other SMTs at 1–27 (median 14) years from the original diagnosis of Hodgkin's disease. Ten year survival from the date of diagnosis of a SMT (n = 24) was 45%. All patients who developed acute leukemia died from that cause within 6 months. The 10 year survival for patients with other tumours (n = 18) was 61% (Fig. 6). All six patients with leukemia developed this complication following the treatment of relapsed Hodgkin's disease, one patient after a single relapse and five patients after multiple relapses. The latter patients had received multiagent chemotherapy combined with irradiation on multiple occasions. None of 196 patients whose initial treatment included MOPP or MOPP/ABV, 141 patients with stages 1–3B and 55 patients with stage 4 disease developed leukemia as an isolated first event.

The initial treatment of basal cell carcinoma (five patients) and thyroid carcinoma (four patients) was successful and these patients remained SMT relapse free. Three patients died from an uncontrolled SMT: sarcoma (one patient), melanoma (one patient), and breast cancer (one patient). Three patients died from toxicity, one patient with histiocytosis X from disseminated varicella during active treatment of uncontrolled Hodgkin's disease, one patient from sepsis during treatment of disseminated NHL, and one patient from meningitis 7 years after the diagnosis of a parotid tumour, which was treated by resection and irradiation. In this patient, both the

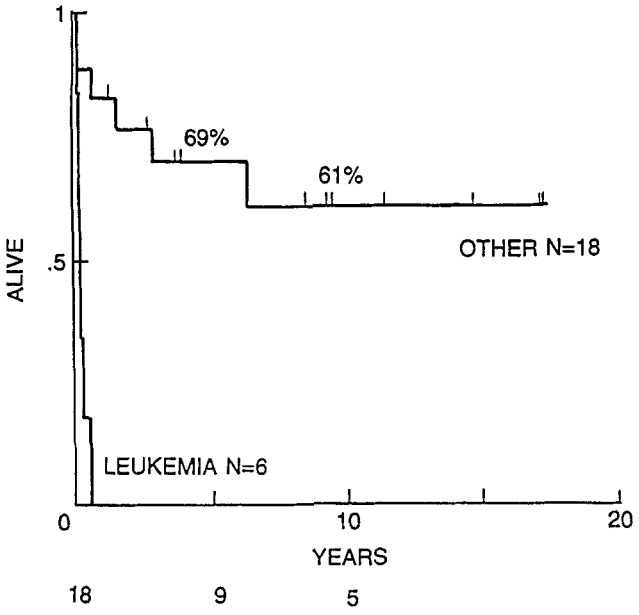

Fig. 6. Survival, measured from the date of diagnosis of a second malignant tumour, by SMT diagnosis: leukemia or other neoplasm.

Hodgkin's disease and parotid carcinoma remained in first remission.

In 16 of 18 SMTs other than leukemia, the tumour was in an irradiated volume, and in one case it was marginal to an irradiated volume. In one case, a patient with melanoma of the leg, the tumour was distant to an irradiated volume. Fourteen of 18 (78%) patients who developed SMTs other than leukemia received multiple agent chemotherapy, either at diagnosis or for relapse, compared overall with 274 of 338 patients (81%).

DISCUSSION

The 20 year SMT incidence of 19% in this series is similar to the LESG incidence of 20%, although both series have some patients in common [12]. A much lower incidence, 1.3% at 10 years from 3 year survival, is reported from Britain [8], but the same 20 year frequency, 20%, was seen in the adult international database [1]. The type of SMTs seen in children with Hodgkin's disease has varied. In this series, leukemia/lymphoma accounted for 8 in 24 (33%) SMTs compared with 20 in 38 (53%) in the LESG [12] and 1 in 6 (17%) in Britain [8], and compared with 264 in 631 (42%) in adults [1]. Thyroid cancer was seen in 4 in 24 (17%) in this series, in 4 in 38 (11%) in the LESG, and none in Britain, compared with 8 in 631 (1%) in adults. Skin cancer (other than melanoma), commonly basal cell carcinoma, was observed in 5 in 24 (21%) in this series, or 7 in 26 (27%) when including third malignancies, compared with 4 in 38 (11%) in the LESG [12], 2 in 6 (33%) in Britain [8], and 45 in 631 (7%) in adults [1].

In these four studies, the respective frequencies for bone and soft tissue sarcomas were 1 in 24 (4%), 4 in 38 (11%), 2 in 6 (33%), and 10 in 631 (2%), and for melanomas 2 in 24 (8%), 0 in 38 (0%), 0 in 6 (0%), and 11 in 631 (2%). There was a major difference in the frequency of other solid tumours, which accounted, respectively, for 4 in 24 (17%), 6 in 38 (16%), and 1 in 6 (17%) in childhood, compared with 293 in 631 (46%) in adults. The common adult cancers of bronchus, breast, large bowel, and small bowel have, to date, rarely been reported as SMTs in children. Breast and colon cancer were each seen once in this series, breast cancer once in the LESG, and no examples were seen in Britain.

The median age at last follow-up of patients in the series was 25 years, so that most patients have not yet entered the years of principal natural risk for the common cancers in adults, and they may yet demonstrate an increased incidence. It is surprising that basal cell cancer of the skin, commonly a disease of the elderly, has been seen so frequently as a SMT in childhood Hodgkin's disease. No genetic association of basal cell cancer and Hodgkin's disease has been described.

In this study the incidence of leukemia plateaued at 4% at 15 years, and the incidence of leukemia plus NHL at 5% at 15 years. This is consistent with previous reports for patients of all ages, which indicated that the principal risk for leukemia is seen 3–9 years after treatment or retreatment of Hodgkin's disease [3,4,15–17]. There were six patients with leukemia observed in this study. All had received systemic treatment substantially in excess of six cycles of MOPP due to one or more relapses. Conversely, it was of particular interest that none of 196 patients in all stages who were treated bimodally at diagnosis developed leukemia as an isolated first adverse event. The duration of follow-up for these patients was 1–23 (median 7) years, so that about one half of these patients have passed the principal risk period for acute leukemia and NHL.

Splenectomy has been reported as a risk factor for leukemia [1,15,18,19]. All six patients who developed leukemia in this study had a splenectomy, but all had also received high total doses of alkylating agents, a major risk factor for leukemia [1,15,16,19,20], as a consequence of one or more relapses.

Two cases of NHL were observed. One occurred as an isolated first event following radiation treatment alone, 8 years from diagnosis, and one occurred 1 year from diagnosis in a stage 4B patient initially treated with seven cycles of MOPP/ABVD and with additional therapy for relapse prior to the development of NHL. As for leukemia, the increased risk of NHL may decrease with time [1,2], but this is not yet certain [4].

Thyroid cancer is a complication of thyroid irradiation

[12,21]. In this series, four patients developed thyroid carcinoma at 7, 9, 14, and 23 years from diagnosis. All received neck irradiation. Two received 25 Gy and 30 Gy combined with six cycles of MOPP, without relapse of Hodgkin's disease, and two patients received 39 Gy and 25 Gy together with additional radiation for relapse. One of these patients was initially treated bimodally.

The low incidence of radiation-induced sarcomas in this report may have been due to the use of low radiation dose, median 27 Gy, at initial treatment. The one patient to develop a sarcoma received high-dose radiation at the sarcoma site as part of retreatment for relapsed Hodgkin's disease.

All but one nonleukemic SMT in this series were associated with previous irradiation of the tissue of origin. We assume there was a causal relationship. However, most SMTs occurred within the trunk or neck, and in EF RT the tissue volume irradiated includes a large fraction of the trunk and neck, so that SMTs at these sites must necessarily be within or marginal to an irradiated tissue volume. There was also a close association of solid SMTs and exposure to MOPP. Since 81% of all patients were exposed to MOPP (or ABVD), we cannot estimate whether this was more than a chance association.

Survival from the date of diagnosis of a SMT, other than leukemia, depended on the nature of the SMT and was not obviously different than that expected for first malignant tumours of the same type occurring at the same age. However, all six patients with leukemia as an SMT died without useful leukemic control. Of the 18 patients with other SMTs, only 3 have died as a consequence of direct progression of the SMT. These were patients with sarcoma, breast cancer, and melanoma. One patient died of toxicity during treatment of the SMT and one from a remote complication (meningitis). The 61% 10 year survival rate from the diagnosis of a solid SMT is superior to the 22% 10 year survival rate for 367 solid SMTs in adults, due to the poor natural survival for many common adult solid tumours, especially lung cancer [1].

Since cumulative treatment intensity is an important risk factor for SMT, the risk of a specific treatment may only be accurately evaluated in patients who never relapse, since subsequent retreatment represents a major change in risk, as is illustrated in this series by the 13%, 20%, and 36% 20 year SMT rates for patients in all stages who either had no, one, or more than one relapse (Fig. 3). This single institution report allowed comparison to be made between two major primary treatment methods for stage 1-3B Hodgkin's disease, laparotomy and splenectomy followed by EF RT (35 Gy) and bimodal treatment, in clinically staged patients, with MOPP (six cycles) and lower dose EF RT (25–30 Gy). For patients who remained disease free in first remission following these regimens, there was no significant difference in the subsequent SMT risk, which was 7% and 3% at 10 years, respectively, with no occurrence of leukemia. The SMT incidence in patients who relapsed following surgical staging, and EF RT was very high, 37% at 20 years, and since 47 of 76 (62%) surgically staged patients relapsed, the overall SMT incidence for this treatment was high, 24% at 20 years.

Bimodal treatment of clinically staged patients replaced EF RT alone in surgically staged patients in Toronto in 1973, principally because of concern for the morbidity and mortality associated with the high relapse rate after EF RT alone [14]. It is now clear that, in addition, there was also major morbidity and mortality associated with an enhanced SMT incidence as a consequence of retreatment. Following sandwich MOPP and EF RT (25–30 Gy), only 16 in 90 (18%) patients in stage 1–3B subsequently relapsed, markedly lowering the morbidity and mortality associated with retreatment. Although introduced 22 years ago, fewer than 10 patients are available for assessment 20 years from diagnosis, so that the SMT incidence at that time cannot be estimated: The overall 10 year SMT incidence for this bimodal treatment was 3%, compared with an overall risk of 11% for patients initially treated with EF RT alone.

Our current treatment for stage 1–3B Hodgkin's disease, MOPP/ABV (three cycles) and EF RT (15 G), was introduced in 1987 to evaluate the effectiveness of low-intensity bimodal treatment in the control of childhood Hodgkin's disease, with a decrease in treatment toxicity, including SMT incidence, being a major objective. It is of interest that at this early point (maximum follow-up 7 years) no toxic deaths or SMTs have occurred (Fig. 4).

The adverse effect of SMTs on survival was demonstrable only in patients in all stages treated from 1963 to 1972, when patients with stage 1–3B disease underwent splenectomy and EF RT alone. For these patients the 20 year survival rate was 54%. When SMT deaths were censored, the survival rate increased to 60%. Fourteen of the 88 patients in this cohort developed at SMT, and eight of these patients died as a consequence of the SMT. It is too early to make a similar comparison in the patients treated bimodally from 1973 to 1983 (n = 114). To date, seven have developed a SMT, but only two have died as a consequence of the SMT.

In this series, patients who relapsed received additional cycles of MOPP (or ABVD) and usually additional radiation treatment. The stepwise increase in SMT rates for patients with no, one, or more than one relapse at 20 years—13%, 20%, and 36% (Fig. 3)—is consistent with a simple cumulative affect of the oncogenic potential of successive, similar bimodal treatment protocols. While we have no formal proof of such a causal relationship, it is a reasonable working hypothesis and is a strong argument favouring the use of initial treatment protocols in children with Hodgkin's disease, which minimize the risk of subsequent relapse.

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